

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION**

Applicant(s): DODDA MOHAN RAO et al.

Serial No: 10/524,478

Group Art Unit: 1626

Filed: 02-11-2005

Examiner: LOEWE, SUN JAE Y

Att. Docket No.: S2096/20001

Confirmation No.: 6950

For: NOVEL CRYSTALLINE FORM OF LINEZOLID

THIRD DECLARATION OF D. MOHAN RAO, PH.D. UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, D. Mohan Rao, a citizen of India, hereby declare and state:

1. I am a co-inventor of the subject matter described and claimed in the present application.

2. I am the Managing Director of Symed Laboratories Limited, with more than 25 years of experience in the Pharmaceuticals Industry. The resume attached as **Appendix 1-A** of the Declaration of D. Mohan Rao, Ph.D. under 37 C.F.R. § 1.132, submitted June 4, 2009 accurately reflects my professional credentials.

3. I have reviewed the present application and its prosecution history including the Office Action of August 21, 2009.

4. I understand from my review of the Office Action in this case that claims 1 and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Barbachyn et al.

5. I understand from my review of the Office Action in this case that claims 1 and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Meng.

6. I understand from my review of the Office Action in this case that claims 1 and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Pearlman et al.

7. I understand from my attorneys that 35 U.S.C. § 102(b) provides:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States[.]

8. I understand from my attorneys that for a prior art reference to anticipate the claims, the reference must teach every element of the claims.

9. The present application claims a crystalline linezolid form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees, and further characterized by an IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm^{-1} , and also wherein there is at least a 99.8% enantiomeric excess of the linezolid form III.

10. The Examiner argues that the information missing from the references is inherently present, e.g. XRD pattern of a solid form. The Examiner admits that the references are silent on this information, but sets forth that Applicant is requested to provide this information in order to show that the instantly claimed crystalline form is not the same as the one disclosed in the prior art.

11. As set forth in the Second Declaration of D. Mohan Rao, Ph.D. Under 37 C.F.R. § 1.132, submitted June 4, 2009, using the methods described in the '478 application, I and/or researchers under my direct supervision prepared linezolid polymorphic form III, and evaluated the linezolid polymorphic form III using X-ray powder diffraction (XRPD) analyses. The XRPD analyses were carried out utilizing a Bruker AXS D8 ADVANCE X-ray powder diffractometer. A 2θ theta continuous scan (1 sec/0.030° step) from 2.00 to 50.000° 2θ was used.

12. The obtained XRPD data for the linezolid polymorphic form III is set forth in Appendix 2–A of the Second Declaration of D. Mohan Rao, Ph.D. Under 37 C.F.R. § 1.132, submitted June 4, 2009, and a copy of which is also submitted herewith as **Appendix 3 - A**.

13. The linezolid polymorphic form III XRPD comprised peaks at about 7.6, 9.6,

13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 deg 2θ.

14. I have carefully reviewed the Barbachyn et.al. reference.

15. The methods as disclosed in the Barbachyn et al. reference does not produce the claimed linezolid polymorphic form III, based on a comparison of the XRPD data for the claimed linezolid polymorphic form III, and the XRPD data for the linezolid polymorphic form produced by the methods of Barbachyn.

16. Using the methods described in the Barbachyn reference, I and/or researchers under my direct supervision prepared the linezolid polymorphic form, and evaluated the linezolid polymorphic form produced using the methods of Barbachyn.

17. The XRPD data of linezolid polymorphic form produced using the methods of Barbachyn is attached as **Appendix 3 - B**.

18. The linezolid polymorphic form produced using the methods of Barbachyn has peaks at 9.513, 13.868, 14.207, 16.189, 16.792, 19.417, 19.901, 21.567, 22.368, 22.816, 23.493, 25.262, 27.018, 28.878, 37.024 degrees 2θ.

19. A comparison of the XRPD data for the claimed linezolid form III, the measured XRPD data of linezolid form III, and the linezolid polymorphic form produced using the methods of the Barbachyn reference is set forth in **Appendix 3 - C**.

20. Accordingly, I believe that the facts support a conclusion that the methods as disclosed in the Barbachyn et al., reference do not produce the claimed linezolid polymorphic form III, based on a comparison of the XRPD data for the claimed linezolid polymorphic form III, and the linezolid polymorphic form produced using the methods of Barbachyn.

21. I have carefully reviewed the Meng reference.

22. The methods as disclosed in the Meng reference does not produce the claimed linezolid polymorphic form III, based on a comparison of the XRPD data for the claimed linezolid polymorphic form III, and the XRPD data for the linezolid polymorphic form produced by the methods of Meng.

23. Using the methods described in the Meng reference, I and/or researchers under

my direct supervision prepared the linezolid polymorphic form, and evaluated the linezolid polymorphic form produced using the methods of Meng.

24. The XRPD data of linezolid polymorphic form produced using the methods of Meng is attached as **Appendix 3 - D**.

25. The linezolid polymorphic form produced using the methods of Meng has peaks at 9.507, 13.864, 14.206, 16.213, 16.770, 19.903, 21.575, 22.381, 22.802, 23.510, 25.270, 27.012, 28.877, 37.017 degrees 2 θ .

26. A comparison of the XRPD data for the claimed linezolid form III, the measured XRPD data of linezolid form III, and the linezolid polymorphic form produced using the methods of the Meng reference is set forth in **Appendix 3 - E**.

27. Accordingly, I believe that the facts support a conclusion that the methods as disclosed in the Meng reference do not produce the claimed linezolid polymorphic form III, based on a comparison of the XRPD data for the claimed linezolid polymorphic form III, and the linezolid polymorphic form produced using the methods of Meng.

28. I have carefully reviewed the Pearlman et al. reference.

29. The methods as disclosed in the Pearlman et al. reference does not produce the claimed linezolid polymorphic form III, based on a comparison of the XRPD data for the claimed linezolid polymorphic form III, and the XRPD data for the linezolid polymorphic form produced by the methods of Pearlman.

30. Using the methods described in the Pearlman reference, I and/or researchers under my direct supervision prepared the linezolid polymorphic form, and evaluated the linezolid polymorphic form produced using the methods of Pearlman.

31. The XRPD data of linezolid polymorphic form produced using the methods of Pearlman is attached as **Appendix 3 - F**.

32. The linezolid polymorphic form produced using the methods of Pearlman has peaks at 9.537, 13.895, 14.227, 16.200, 16.781, 19.417, 19.925, 21.577, 22.380, 22.837, 23.507, 25.281, 27.033, 28.897, 37.051 degrees 2 θ .

33. A comparison of the XRPD data for the claimed linezolid form III, the measured

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

XRPD data of linezolid form III, and the linezolid polymorphic form produced using the methods of the Pearlman reference is set forth in **Appendix 3 - G**.

34. Accordingly, I believe that the facts support a conclusion that the methods as disclosed in the Pearlman reference do not produce the claimed linezolid polymorphic form III, based on a comparison of the XRPD data for the claimed linezolid polymorphic form III, and the linezolid polymorphic form produced using the methods of Pearlman.

35. Accordingly, since Barbachyn et al., Meng, and Pearlman et al. does not teach every element of the claims, the claims are not anticipated.

*

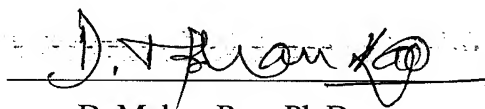
*

*

36. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date:

21/11/2009


D. Mohan Rao, Ph.D.

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

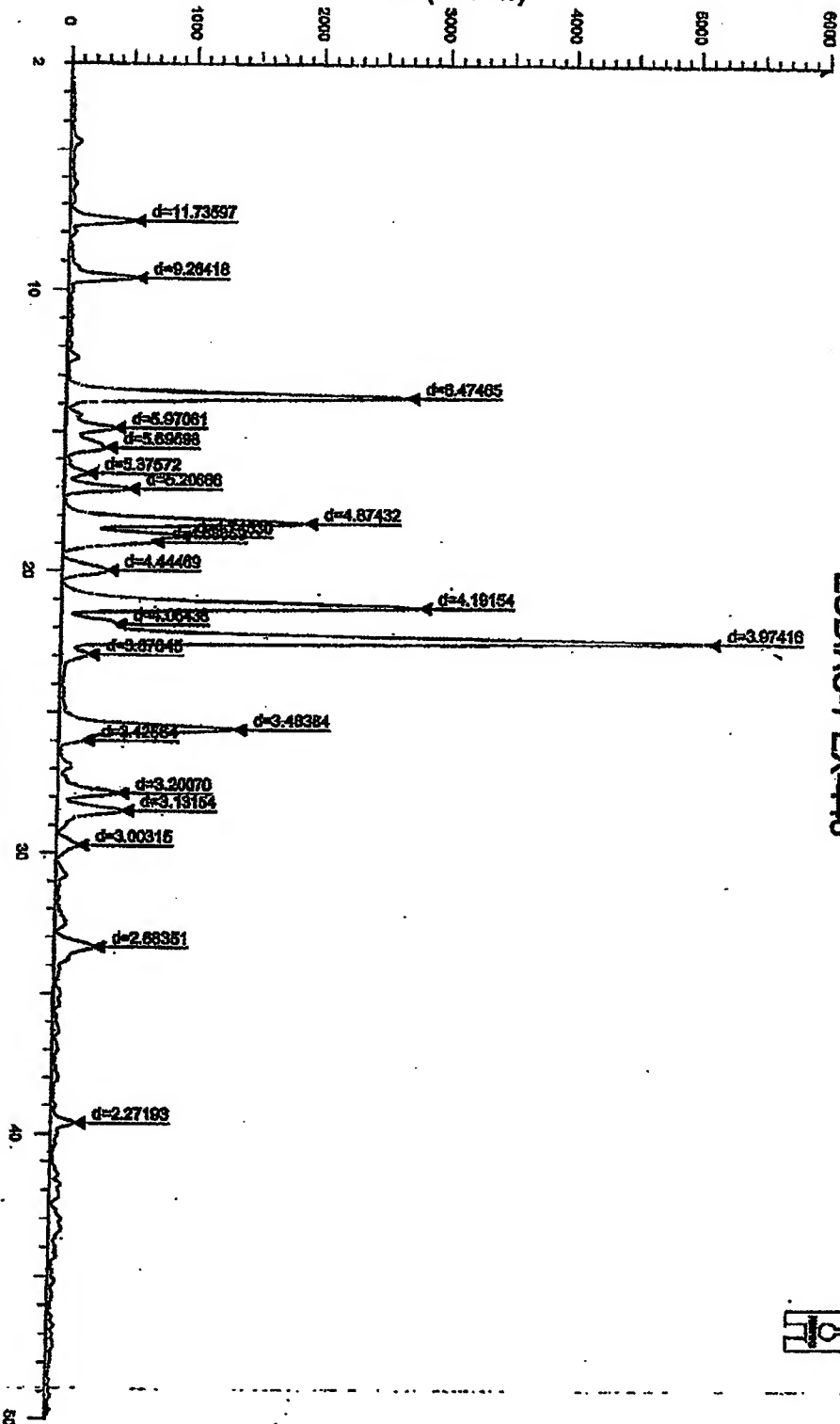
Appendix 3 - A

Figure 1

Lin (Counts)

File: ZODIAC-7 EX-448.raw - Type: 2Th/Th locked - Start: 2.000 - End: 50.000 - Step: 0.030 - Stop time: 1. s - 2-Theta: 2.000 - Th: 1.000 - Creation: 03-Apr-04 16:41:05
Operations: Smooth 0.150 | Background 0.877, 1.000 | Import

2-Theta - Scale



ZODIAC-7 EX-448



Tested by: SE

3 April 2004

Checked by: SE

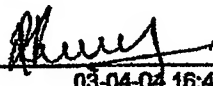
3 April 2004

Product Name : ZODIAC-7 EX-448

File Name : C:\DIFFDAT\ZODIAC-7 EX-448 raw

SNo.	Angle 2-Theta °	d value Angstrom	Intensity % %
1	7.527	11.73597	9.80
2	9.539	9.26418	10.20
3	13.666	6.47466	52.30
4	14.825	5.97081	7.20
5	15.544	5.69598	6.00
6	16.477	5.37572	3.10
7	17.016	5.20666	9.60
8	18.185	4.87432	37.10
9	18.684	4.74530	17.50
10	18.920	4.68669	13.80
11	19.960	4.44469	6.50
12	21.179	4.19154	54.90
13	21.850	4.06438	8.10
14	22.352	3.97416	100.00
15	22.923	3.87645	3.90
16	25.548	3.48384	26.90
17	25.958	3.42968	3.90
18	27.852	3.20070	9.00
19	28.480	3.13154	9.80
20	29.726	3.00315	3.00
21	33.363	2.68351	5.70
22	39.638	2.27193	3.40

Tested by : SPB
03-04-04 16:45

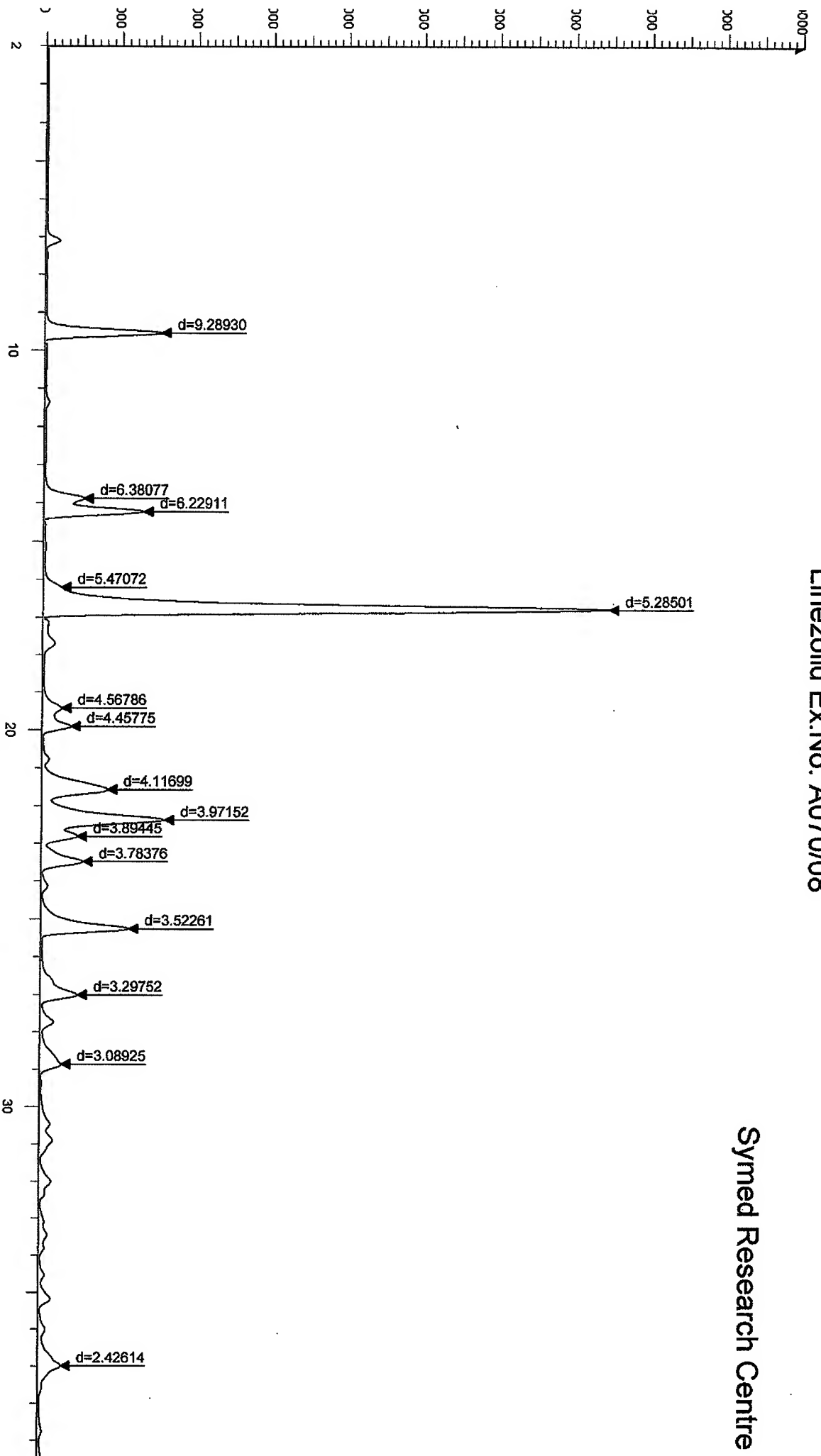
Checked by : 
03-04-04 16:45

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

Appendix 3 – B

Linezolid Ex.No: A070/08

Symed Research Centre



Linezolid Ex.No: A070/08 - File: LIN10100901.raw - Start: 2.000 ° - End: 39.986 ° - Step: 0.030 ° - Step time: 38. s - 2-Theta: 2.000 ° - Theta: 1.000 ° - Creation: 10/10/2009 10:12:58
Operations: Smooth 0.157 | Background 1.000,1.000 | Import

Tested by: Shreya
Date: 10.10.08

Checked by: Blair
Date: 10/10/2009

Product Name : Linezolid Ex.No: A070/08

File Name : LIN10100901.raw

S.No	Angle 2-Theta °	d value Angstrom	Intensity %
1	9.513	9.28930	20.30
2	13.868	6.38077	6.80
3	14.207	6.22911	17.40
4	16.189	5.47072	3.00
5	16.762	5.28501	100.00
6	19.417	4.56786	3.20
7	19.901	4.45775	4.80
8	21.567	4.11699	11.30
9	22.368	3.97152	21.40
10	22.816	3.89445	6.00
11	23.493	3.78376	7.10
12	25.262	3.52261	15.20
13	27.018	3.29752	6.30
14	28.878	3.08925	3.50
15	37.024	2.42614	3.70

Tested by: ShawelDate : 10.10.09Checked by: PooleyDate : 10/10/2009

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

Appendix 3 – C

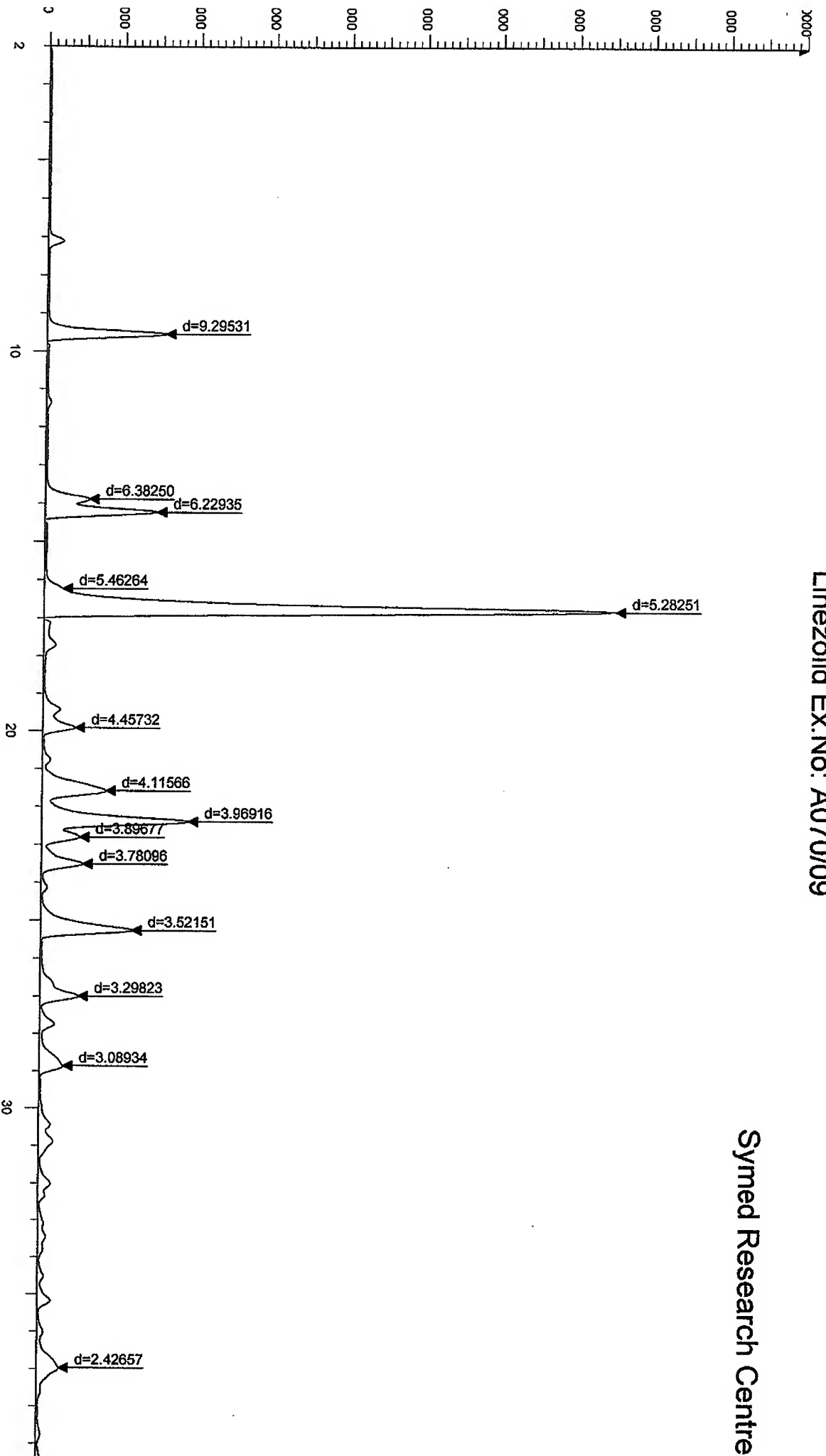
Linezolid Form III (20 Values)	Linezolid Form III (20 Values) Measured	Barbachyn Linezolid (20 Values)
7.6	7.527	
9.6	9.539	9.513
13.6	13.666	13.868
14.9	14.825	14.207
	15.544	
	16.477	16.189
	17.016	16.792
18.2	18.185	
18.9	18.684	
	18.920	
	19.960	19.417
21.2	21.179	19.901
	21.850	21.567
22.3	22.352	22.368
	22.923	22.816
		23.493
25.6	25.548	25.262
26.9	25.958	
27.9	27.852	27.018
	28.480	28.878
29.9	29.725	
	33.363	
		37.024
	39.638	

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

Appendix 3 – D

Linezolid Ex.No: A070/09

Symed Research Centre



Linezolid Ex.No: A070/09 - File: LIN10100902.raw - Start: 2.000 ° - End: 39.986 ° - Step: 0.030 ° - Step time: 38. s - 2-Theta: 2.000 ° - Theta: 1.000 ° - Creation: 10/10/2009 10:28:26
Operations: Smooth 0.157 | Background 1.000,1.000 | Import


Tested by: Shahid
Date: 10.10.09

Checked by: Shahid
Date: 10/10/2009

Product Name : Linezolid Ex.No: A070/09

File Name : LIN10100902.raw

S.No	Angle 2-Theta °	d value Angstrom	Intensity % %
1	9.507	9.29531	20.60
2	13.864	6.38250	7.40
3	14.206	6.22935	19.30
4	16.213	5.46264	3.00
5	16.770	5.28251	100.00
6	19.903	4.45732	5.40
7	21.575	4.11566	10.80
8	22.381	3.96916	25.30
9	22.802	3.89677	6.30
10	23.510	3.78096	6.90
11	25.270	3.52151	15.60
12	27.012	3.29823	6.40
13	28.877	3.08934	3.80
14	37.017	2.42657	3.50

Tested by: Date : 10.10.09Checked by: Date : 10/10/2009

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

Appendix 3 – E

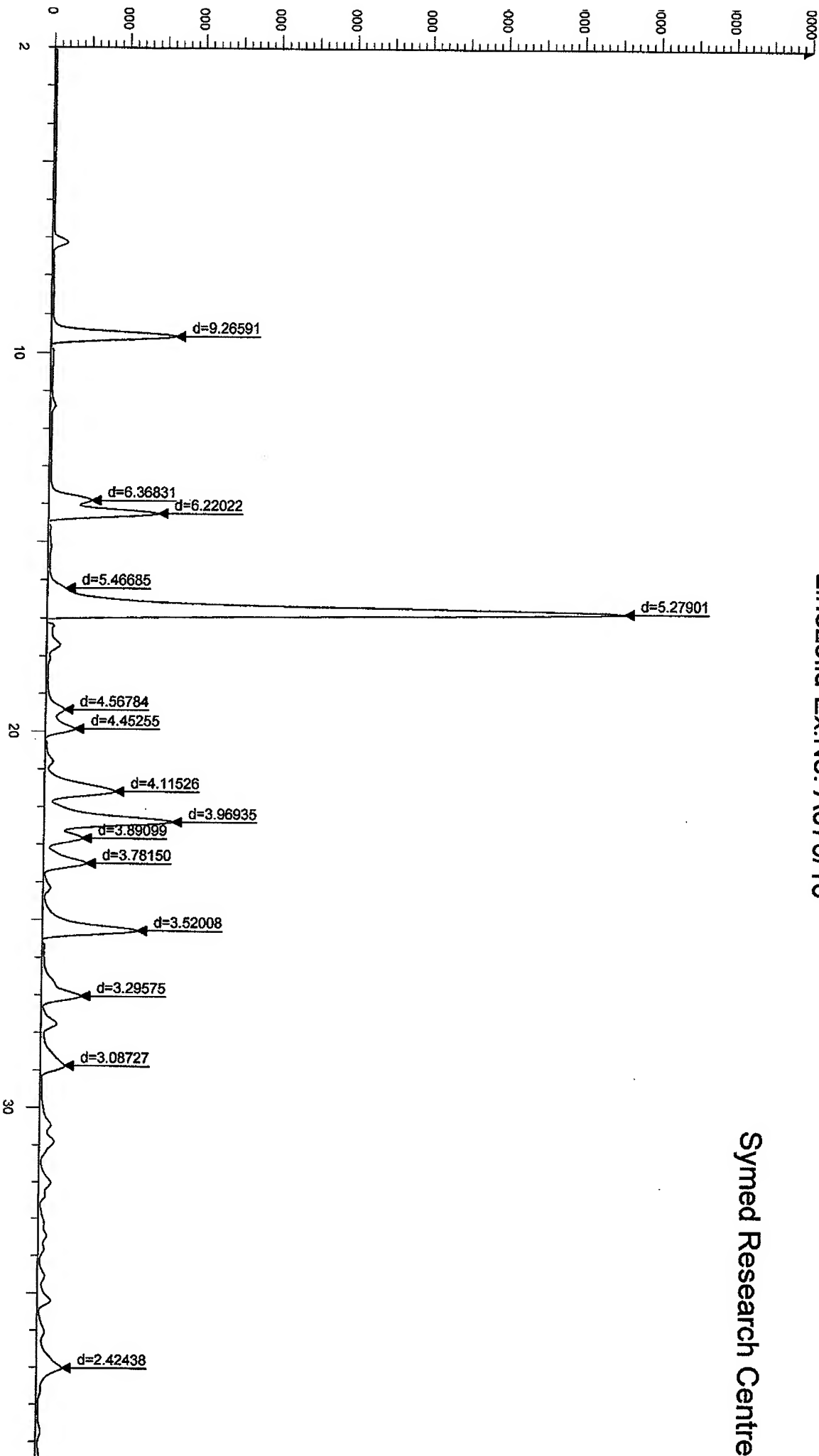
Linezolid Form III (20 Values)	Linezolid Form III (20 Values) Measured	Meng Linezolid (20 Values)
7.6	7.527	
9.6	9.539	9.507
13.6	13.666	13.864
14.9	14.825	14.206
	15.544	
	16.477	16.213
	17.016	16.770
18.2	18.185	
18.9	18.684	
	18.920	
	19.960	19.903
21.2	21.179	21.575
	21.850	
22.3	22.352	22.381
	22.923	22.802
		23.510
25.6	25.548	25.270
26.9	25.958	
27.9	27.852	27.012
	28.480	28.877
29.9	29.725	
	33.363	
		37.017
	39.638	

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

Appendix 3 – F

Linezolid Ex.No: A070/10

Symed Research Centre



2-Theta - Scale

Linezolid Ex.No: A070/10 - File: LIN10100903.raw - Start: 2.000 ° - End: 39.986 ° - Step: 0.030 ° - Step time: 38. s - 2-Theta: 2.000 ° - Theta: 1.000 ° - Creation: 10/10/2009 10:42:35
Operations: Smooth 0.157 | Smooth 0.157 | Background 1.000,1.000 | Import

Tested by: Shweta
Date: 10.10.09

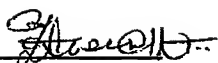
Checked by: Shweta
Date: 10/10/2009

Product Name : Linezolid Ex.No: A070/10

File Name : LIN10100903.raw

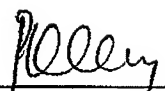
S.No	Angle 2-Theta °	d value Angstrom	Intensity %
1	9.537	9.26591	21.40
2	13.895	6.36831	7.10
3	14.227	6.22022	18.80
4	16.200	5.46685	2.90
5	16.781	5.27901	100.00
6	19.417	4.56784	2.90
7	19.925	4.45255	4.80
8	21.577	4.11526	11.80
9	22.380	3.96935	21.90
10	22.837	3.89099	6.30
11	23.507	3.78150	7.10
12	25.281	3.52008	16.10
13	27.033	3.29575	6.50
14	28.897	3.08727	3.80
15	37.051	2.42438	4.00

Tested by:



Date : 10.10.08

Checked by:



Date : 10/10/2009

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

Appendix 3 – G

Linezolid Form III (20 Values)	Linezolid Form III (20 Values) Measured	Pearlman Linezolid (20 Values)
7.6	7.527	
9.6	9.539	9.537
13.6	13.666	13.895
14.9	14.825	14.227
	15.544	
	16.477	16.200
	17.016	16.781
18.2	18.185	
18.9	18.684	
	18.920	
	19.960	19.417
21.2	21.179	19.925
	21.850	21.577
22.3	22.352	22.380
	22.923	22.837
		23.507
25.6	25.548	25.281
26.9	25.958	
27.9	27.852	27.033
	28.480	28.897
29.9	29.725	
	33.363	
		37.051
	39.638	